Remarks

Page 23 is amended a second time to identify TITERMAX® as a "blockcopolymer/metabolizable oil" adjuvant, as requested by the Examiner. It is believed all other trademarks in the Specification are properly used and generically defined.

Claim 27 is amended to recite an immunogenic composition comprising *L. intracellularis* antigen that has all the immunogenic characteristics of ATCC No. 55370, that is inactivated and that induces production of protective antibodies to at least one *L. intracellularis* antigen from the group 21, 31, 41, 43, 33, 60, 71 and 115 kDa. A protective, inactivated *L. intracellularis* composition is unexpected, particularly as this is an obligate, intracellular, parasitic bacterium.

In the Final Office Action of October 10, 2002, the Examiner maintained the rejection under 35 USC 102 over Jones et al US Patent 5,601,059, concluding that in the disclosed examples, in which a tissue culture grown *L.intracellularis* is used to infect swine, the swine inherently produced antibodies. The Examiner stated the opinion that the use of the term "vaccine"

in the claims is an intended use and does not distinguish over the composition of Jones et al. The same basis is used by the Examiner for rejecting the claims under 35 USC 103(a) over Joens et al, as well. The Examiner further objected to Claim 27 for being drawn to a non-elected invention, interpreting the claim to not being drawn to whole culture vaccines and inactivated whole culture vaccines.

Rejections over Joens et al under 35 U.S.C. § 102 and 35 U.S.C. § 103, as well as the objection to Claim 27, are respectfully traversed. Administering an organism to an animal to prove that the organism can infect the animal in no way suggests that a vaccine to protect the animal can be developed. Applicant has demonstrated that his inactivated vaccine protected swine on challenge (Example 3, beginning p. 22 and TABLE 1) Before that, there was no reasonable assurance that this could be done.

Use of the term "vaccine" is not an intended use, it specifically characterizes the composition claimed. To be even more specific, however, "vaccine" has now been replaced with "immunogenic composition." Even if "vaccine" was not believed to be a limitation, the claimed composition comprises, in addition to the

antigen, an adjuvant. The infectious composition administered in the example (example 2) of the '059 patent did not include and adjuvant.

It should be noted, moreover, that the claimed composition is characterized, and limited, by causing the production of antibodies to very specific antigens, the 21 kDa, 41 kDa, 43 kDa, 44 kDa, 60 kDa, 71 kDa, and 115 kDa antigens defined in the present specification. These antigens were not defined or suggested in the '059 patent. In this regard, Applicant determined that these antigens are the antigens that react with protective antibodies. Infecting, not immunizing, swine as described in the '059 patent, would not lead the skilled practitioner to conclude that protective antibodies were assuredly raised, nor would these antigens be identified.

The Examiner improperly discards Applicant's argument that the discussion of vaccine antigens in the '059 patent is speculative. There was no description of the preparation of an actual vaccine or the showing that an effective vaccine could be produced let alone the identification of specific antigens.

Applicant presently claims a proliferative ileitis immunogenic composition that he has shown can be made and provide protection to immunized animals against direct challenge (Example 3 and TABLE 1). That this could be accomplished cannot be concluded from the disclosure in the '059 patent, for which he is co-inventor. That patent is directed to isolation and characterization of the infectious agent, and to finding a cell line in which the obligate, intracellular parasitic bacterium could be grown in cell culture. An important step, but not the achievement of a protective vaccine composition.

It goes without saying that if the production of an effective vaccine was a given once a causative organism is isolated and characterized, a vaccine would be available for every major infectious disease, and this has not occurred despite years of effort in the medical and research communities.

As stated by Applicant in the present Specification: "[i]t is understood by those skilled in the art that neither the growth of an organism nor the identification of antigen(s) from that organism can assure that a vaccine can be produced." (page 6, lines 15-17). Identifying the organism and speculating

that a vaccine could be made does not place the achievement of formulating a protective immunogenic composition in the hands of the ordinary practitioner.

This is particularly true in the present case, *L. intracellularis* is an obligate, intracellular, parasitic bacterium. Unlike most disease causing bacteria, it must live within a certain part of the cell to function. There is even less expectation of providing an effective vaccine, a protective immunogenic composition, for a parasitic intracellular bacterium than for others. It is unexpected to produce an inactivated, immunogenic composition that induces the production of protective antibodies, as the bacterium is normally present in the cell during its life cycle. Applicant claims, not just a composition comprising the *L.intracellularis* antigen, he claims a composition comprising the antigen and an adjuvant characterized by inducing an immunized swine to produce antibodies that react with specific antigens. With the present amendment, the composition is limited to being inactivated, it is required to induce the production of protective antibodies to specific antigens, and the strain of *L. intracellularis* must have all the immunogenic

characteristics of ATCC deposit No. 55370. No composition having these characteristics is taught by Joens et al '059 or anywhere in the prior art.

In view of the above, it is believed that claims 3-5, 27-29 and 31 are in condition for allowance. Favorable action is solicited. Should the Examiner consider that a conference would be helpful in advancing the prosecution of the application, he is invited to telephone Applicant's attorney at the number below.

Respectfully submitted,

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in an atmosphere of CO_2:O_2N_2 (8:8:84). Supernat was removed and the cells were treated with 0.2% KCL for 5 min. and 0.1% KCL for 25 min. The KCL was removed and the cells were harvested by scraping. The harvested cells were passed through a 22 gauge needle to break down the cell structure. The cell lysate was subjected to low speed centrifugation for 10 min. and the semi-purified organisms remaining in the supernatant were harvested by high speed centrifugation. Antigen was pooled from 25 flasks and a portion of the antigen was subjected to a french press treatment for the production of soluble antigen. The Reminder was aliquoted and stored at -70°C. This soluble antigen was formulated into a vaccine according to the following procedure. Vaccine antigen was formulated with TITERMAX®, a block copolymer/metabolizable oil adjuvant or Freunds Incomplete adjuvant at a concentration of 500ug of antigen/dose. With the TITERMAX® adjuvant, 0.5mL was mixed with 0.5mL of antigen to produce a 1.0mL dose containing 500ug of antigen. With the Freunds Incomplete adjuvant, 2.0 mL of adjuvant was mixed with 2.0 mL of antigen such that the total dose also contained 500ug.

In order to determine whether the antigen produced could protect pigs from a homologous challenge or from exposure to heterologous isolates or strains, ten 4-week-old pigs were vaccinated and later challenged. Ten control pigs received equal doses of a mock vaccine which contained only the tissue culture medium Minimal Essential Medium (MEM)) and adjuvant (without antigen). The vaccine used for the first vaccination contained TITERMAX® adjuvant while the vaccine used for the second vaccination contained Freunds Incomplete adjuvant. Serum samples were taken prior to vaccination (prebleed), at day of booster (Day 14) and at the day of challenge (Day 35) to demonstrate the production of an immune response post vaccination. Serum was tested for antibody to *L. intracellularis* via an ELISA wherein the wells in a 96-well plate were coated with *L. intracellularis* antigen (purified from pig gut epithelial cells) of a clinical isolate which was from a different source than the isolate used to produce the vaccine. Therefore, presence of an

In the Claims (Marked Version)

3. (amended) The [proliferative ileitis vaccine] immunogenic composition according to Claim 27 further comprising an inactivating agent.

4. (amended) The [proliferative ileitis vaccine] immunogenic composition according to Claim 3, wherein the inactivating agent is selected from the group consisting of formalin, beta-propiolactone, heat, binary ethylenimine, detergents, and freeze/thaw.

5. (amended) The [proliferative ileitis vaccine] immunogenic composition according to Claim 3, wherein the adjuvant is selected from the group consisting of polymers, oil in water, water-in-oil-in-water, lipids, aluminum hydroxide, aluminum phosphate, aluminum sulfate, immunomodulators and combinations thereof.

27. (amended) An immunogenic composition [A proliferative ileitis vaccine] comprising inactivated *L.intracellularis* antigen, wherein the *L.intracellularis* has all the immunogenic characteristics of ATCC deposit No. 55370, and an adjuvant, and wherein the [vaccine] immunogenic composition induces an immune response resulting in the production of protective antibodies in a swine to which it has been administered that react with at least one antigen selected from the group consisting of *L.intracellularis* ATCC deposit No. 55370 antigens having the molecular weights of 21 kDa, 31 dDa, 41

kDa, 43 kDa, 44 kDa, 60 kDa, 71 kDa, and 115 kDa [and greater than 115 kDa].

28. (amended)The [proliferative ileitis vaccine] immunogenic composition according to claim 27, wherein the *L.intracellularis* antigen comprises lysate of whole tissue culture grown *L. intracellularis.*

29. (amended) The [proliferative ileitis vaccine] immunogenic composition according to claim 27, wherein the *L. intracellularis* antigen comprises an inactivated tissue culture of *L.intracellularis.*

31. A method for protecting swine from disease caused by *L. intracellularis* comprising, administering to said swine an effective amount of the [vaccine] immunogenic composition according to claim 27.